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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/341,505	07/12/1999	STEPHEN PHILIP JACKSON	MEWE-005	5221

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BOZICEVIC, FIELD & FRANCIS LLP
200 MIDDLEFIELD RD
SUITE 200
MENLO PARK, CA 94025

EXAMINER	
LIU, SAMUEL W	
ART UNIT	**PAPER NUMBER**
1653	27

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/341,505	JACKSON ET AL.	
	Examiner	Art Unit	
	Samuel W Liu	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3 and 6-28* is/are pending in the application.

4a) Of the above claim(s) *5,7-18,20,21,23,24 and 26-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,6,19,22 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *PCT/GB98/00095* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's request for continued examination of the current application filed 9 July 2002 (paper 25) has been received and entered. Also, the response filed on 9 January 2002 (paper 26) with respect to cancellation of Claims 2 and 4 and amendment of Claims 1, 3, 6, 19, 22 and 25, and applicant's petition for extension of time of one month have been entered. Claims 1, 3 and 6-28 are pending according to the current statutes of this application. Claims 1, 3, 6, 19, 22 and 25 are examined in this Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 6, 19, 22 and 25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for determining biological activity of XRCC4 (a 38KDa nuclear phosphoprotein) and determining biological activity of DNA ligase IV (Examples 1 and 2), and producing peptide variants based on XRCC4 and DNA ligase IV proteins, does not reasonably provide enablement for a method of identifying a compound that negatively regulates Interactions between interaction between XRCC and DNA ligase IV, or between XRCC4 and DNA-PKcs/Ku (DNA-dependent protein kinase catalytic subunit - Ku86/Ku70) (note that Ku stands for Ku86/Ku70heterodimer), or between any two proteins from (1) XRCC, (2) DNA ligase, (3) DAN-PKcs/Ku complex, (4) DNA-PKcs and (5) Ku factors. The specification does

not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant application is directed to a method for screening for an inhibitory compound X that affects the interactions as stated above. The compound represents a genus encompasses peptide variants and non-peptide nature molecules, and a substance including from a drug to a non-peptide carrier molecule (see page 16-19). Since unpredictability of the subject compound to be screened and identified, adequate written description requires more than a mere statement that it is part of invention. The specification disclosure of the current application is insufficient to enable skilled artisan to practice the invention as broadly claimed without an undue amount of experimentation.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *in re* Wands 8 USPQ2d 1400, 1400 (Fed. Cir. 1998). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include but not limited to: 1) the nature of the invention; 2) the breath of the claims; 3) the predictability or unpredictability of the art; 4) the amount of direction or guidance presented; 5) the presence or absence of working examples; 6) the quantity of experimentation necessary; 7) the relative skill of those skilled in the art.

Each factor is addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

(1) The nature of the invention/The scope of the claims:

The current application is directed to a method of screening for an inhibitory compound X that affects the interactions between proteins: XRCC4, DNA ligase IV, AND-PKcs and Ku heterodimer. The specification sets forth a compound (agent) is derived from a peptide sequence of XRCC$ protein or DNA ligase IV (see page 16, lines 9-12); the compound encompasses is peptide variants or derivatives (see page 16, lines 19-24, and pages 17-18). The variants include (1) any types of mutants of the wild-type protein e.g. addition, insertion, deletion and substitution, (2) naturally-occurring allelic mutants (see page 16, lines 25-32), (3) a larger fusion protein, and (4) non-peptide mimetics or a substance (see page 18, lines 3-4), including substance produced by peptide linkage to a molecule encompassing a label, a drug, a toxin, a carrier, a transport molecule and antibody or binding fragment of the antibody thereof (see page 18, the second and the last paragraphs). Because the genus (a compound) is so broad and unpredictable as to a common attribute to inhibition of the interactions between the proteins (see the foregoing statement) that the skilled artisan would have not known what type(s) of compounds is/are to be synthesized or recombinantly produced or recombinantly produced which is followed by chemical modification in order to produce a group of the compound being subject to screening their inhibitory ability with respect to regulation of the above-mentioned interactions.

Note that the interactions between or/and among XRCC4, DNA ligase IV, DNA-PKcs and Ku proteins count up to at least six combinations. Chen, L. et al. (J. Biol. Chem. (2000) 275, 16196-26205) demonstrate that DNA ligase IV-XRCC4 and DNA-PKcs also formed complexes in the presence of DNA molecules. Thus, involvement of multiple proteins (≥ 2) in screening the

claimed compound X would augment complexity degree as well as unpredictability of the outcome of the screening method.

The claims of the current application recite "a compound" which reads on any biomolecule, organic, or inorganic, or chelating compound (e.g. an organic molecule coordinated to zinc or other transition state metal ion). Therefore, the compound is so varied and broad that the scope of claims is outside the bounds of the enablement and would have resulted in the necessity of undue experimentation.

(2) The unpredictability of the art:

As stated above, since the compound is highly variant encompasses peptide, non-peptide or other undefined bio- or/and organic molecules, the method developing for screening these molecules is unpredictable absent factual indicia to the contrary.

(3) The state of the prior art:

The general knowledge and level of skilled in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Because, as mentioned in the foregoing, the number of compounds to be screened and identified for their ability of inhibition of the interactions above-mentioned is exceeding large and variant; thus the method to be developed for these "compound X" molecules would be numerous and variant.

Further, in consideration of involvement of DNA ligase IV, XRCC4, DNA-PKcs, and Ku proteins in cellular (*in vivo*) double stand DNA repair event, the interaction of the proteins with DNA molecule is a determining factor for evaluating the inhibitory activity of the identified compound. McElhinny, S. A. N. et al. (*Mol. Cell. Biol.* (2000) 20, 2996-3003) teach that XRCC4's DNA binding helps stabilize the ternary [XRCC4-DNA ligase IV-Ku], i.e. protein-

DNA interaction has an impact on the interactions between the proteins above-mentioned. Because the current invention sets forth that the compound (agent) are useful in treatment of disease states, cancer, retroviral infections etc. (see abstract and page 9), the compound should be identified and characterized in the level involving the DNA-protein interaction insofar as *in vivo*. The current application is silent in teaching, guidance, and examples as to assay for the compound interfering with the subject protein interaction(s) in the presence of a ds-DNA fragment. For this regard, upon having identified compound(s), the skilled artisan is also required to conduct undue experimentation to inspect the inhibitory activity in the presence of the DNA molecule, which would mimic XRCC4/DNA ligase IV/DNA-PKcs/Ku involved *in vivo* ds-DNA repair and be applicable to DNA repair related disease state.

(4) The quantity of experimentation necessary:

In the absence of working examples with regard to the above mentioned a unpredictable variants and outcome of screening/charactering the variants, unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention. Because of the reasons set forth in the forgoing, the quantity of experimentation would be large and of unpredictability. The skilled artisan would be required to carry out a large body of pre-search for a group of compounds which are obtainable or producible.

(5) The relative skill of those in the art:

The general knowledge and level of skill in the art do not supplement the omitted description with respect to an unpredictable number of compound X variants or derivatives. In view of the preceding factors (1-4), the level of skill in this art is high and requires at least a

peptide biochemist and pharmacologist and molecular biologist at Ph.D. level with several years of experience in protein chemistry as well as knowledge in peptide synthesis, organic synthesis, and mutagenesis; yet, even with a level of skill in the art as those mentioned in precedence, predictability of the results is still highly variable. See at pages 9-10 of this office action.

The currant application sets forth that the compound inhibits DNA ligase IV activity (see Claims 3 and 22). To screen and characterize the candidate molecule of the inhibitory activity, constant the physical and biochemical properties of ligase molecule is necessary. Grawunder, U. et al. (*Nature* (1997) 388, 492-495) show that ligation activity DNA ligase IV is increased five-fold by a and seven- to eightfold when XRCC4 is co-expressed with DNA ligase IV. Thus, the mean of production of the assayed ligase has dramatically impact on screening and characterizing the compound. Teaching, direction and any working examples as to this aspect is missing form the specification of the instant application. Thus, even an artisan who possesses knowledge and skills as mentioned in precedence will be unable to supply what is missing herein above.

In consideration of each of factors stated above, absent factual data to the contrary, the amount and level of experimentation needed is undue.

Applicants' comments (pages 3-4) in the response filed 9 July 2002 has been fully considered but they are not persuasive.

Applicants assert that the present claims are directed to methods of screening for inhibitory compounds that are only identified as a result of the method, and that any compounds used in the method may be tested for inhibitory activity using the present methods and the compounds are not limited to any particular class of compounds and the compounds can be non-

inhibitory molecules. The current application is directed to an *in vitro* method of screening, identifying and characterizing the inhibitory activity of the tested compounds. In order to accomplish the method, all the subject proteins (DNA ligase IV, XRCC4, DNA-PKcs, and Ku proteins) have to be isolated and purified and the tested compounds have to be synthesized by (a) a recombinant approach, or (b) by organic synthesis, or combination of both (a) and (b).

As stated in the foregoing, the "compound X" as claimed encompasses various classes of molecules (e.g. peptide, non-peptide, and any substance including drug, toxin, carrier molecule and their peptide conjugates thereof etc.) and numerous molecules (a compound library). Thus, selection of compounds out of such the compound library would not be predictable which in turn renders the method outcome for identifying inhibitory candidate compounds unpredictable. The compound X, a genus, is so variant and broad as to what it encompasses that the scope of claims is outside the bounds of the enablement and would have resulted in the necessary of undue experimentation.

Applicants also assert that the specification provides a complete teaching to the person skilled in the art regarding the classes of compound have been discussed in the specification referring to (1) page 15 line 26 to page 16 line 35, where the specification sets forth any possible types of peptide mutants, e.g. addition, deletion, insertion and substitution, naturally occurring allelic mutations and alanine scanning mutagenesis. Note that the application does not provide teaching or guidance as to how to select and make these variants or mutant compounds in the claimed method. The skilled artisan would not know which mutation approaches are applicable for selecting subject compounds from the different compound classes (e.g. peptide variants, non-peptide derivatives, naturally-occurring allelic mutants of XRCC4 and DNA ligase IV proteins)

(see the above). In addition, multiple interaction (i.e. binding involves more than two protein factors, e.g. DNA ligase IV – XRCC4 forms a complex with the third molecule, DNA-PKcs (see the foregoing statement); the skilled artisan would not know whether or not the screening for the inhibitory compounds are involved in bimolecular protein-protein interaction, or ternary, or even quaternary interaction events. Thus, the method per se is not enabling and requires undue experimentation. (2) page 32 line 16 to 26, where the specification sets forth substances that interfere with the protein interaction as stated above. Note that herein the substances read on any compounds including organic, inorganic and biomolecules. Therefore, the recitation does not support the enablement (see the reasons set forth above). And, (3) page 35 line 34 to page 36 line 3, where enzyme is set forth as an inhibitory compound. Since the current application provide no guidance and example as to which or which kid of enzyme are to be used in the method, it does not support the enablement either (see the reason set forth above).

The response also asserts that the screening methods described in the art (e.g. two hybrid assay as described on page 29 line 35 to page 32 line 4) allow the person skilled in the art to practice the claimed method. This is unpersuasive as well. Two hybrid assay requires making a fusion between interest protein and yeast transcriptional factor Gal4. Note that the fusion protein is a modified recombinant molecule which biological activity identical to authentic protein (unmodified) is unpredictable absent factual indicia to the contrary. The instant application provide insufficient guidance and no working examples as to and design and making of fusion protein, the required experimentation is undue. In addition, peptide compound (if selected) is susceptible to degradation in yeast (see Varshavsky, V (1996) *Proc. Natl. Acad. Sci. USA*. 93, 12142-12149). Furthermore, multiplicity of the interactions ([.g. formation of ternary [XRCC4-

DNA ligase IV-Ku] as taught by McElhinny, S. A. N. et al. (*Mol. Cell. Biol.* (2000) 20, 2996-3003)] would render yeast two hybrid inapplicable. Taken together, the specification does not enable the present claimed invention and would have resulted in the necessary of undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite in the recitation "... being an inhibitor of binding"; does "binding" therein refer to interaction between XPCC4 and DNA ligase IV, or between DNA-PKcs and Ku heterodimer (Ku86 and Ku70), or between Ku86 and Ku70, or between the Ku86/Ku70 heterodimer and XRCC4, or between DNA ligase IV and DNA-PKcs, or between XRCC4 and DNA-PKcs/Ku?

Claim 6 recites "phosphorylation of XRCC4 by DNA-PKcs/Ku"; the recitation is unclear as to whether or not DNA-PKcs alone is able to phosphorylate XRCC4 protein or formation of a DNA-PKcs/Ku complex is required for phosphorylating XCCR4. Also, note that the in the recitation "in the presence and absence of ...", the article "the" is missing preceding to "absence".

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is (703) 306-3483.

The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 703 308-2923. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

SWL

September 27, 2002